REMARKS

Claims 1-27 are pending.

The amendment to claim 19 is editorial. Descriptive support for the amendment to claim 19 can be found in the specification at page 5, lines 7-9.

The amendment to page 4, lines 22-24, of the specification is for correcting a typographical error, 6'-O-carbomoyl-tobramycin, by expressly stating that "6'-O-carbamoyl-tobramycin" means the compound referred to as "6"-O-carbamoyl-tobramycin" in the prior art. Applicants contend that this is not new matter (please see explanations in a response to an indefiniteness rejection below).

The amendments to the paragraph beginning on page 4, line 26 and ending on page 5, line 2, are for grammatical purposes and would not generate new matter.

The amendment to page 6, lines 14-18, of the specification is done to provide, as required by the Examiner, information on the depositary where the two strains of *Streptomyces tenebrarius* disclosed in the specification were deposited.

Claim Rejections -- 35 U.S.C. 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 1-27 as vague because of the recitation "6'-O-carbamoyl tobramycin". Patent applicants are allowed to be their own lexicographers. See MPEP 2111.01. A person skilled in the art would understand the meaning of "6'-O-carbamoyl tobramycin" based on the disclosure in the specification. According to the chemical formula of tobramycin disclosed at the bottom of page 1 of the specification, it is

apparent to the person skilled in the art that only two functional groups, $-NH_2$ and -OH, attached to the number 6 carbon atoms of two glycopyranosyl rings of the "6'-O-carbamoyl tobramycin" molecule can be derivatized. Since the "carbamoyl" portion of the name "6'-O-carbamoyl tobramycin" is preceded with "6'-O-", the artisan would recognize that it is the -OH group attached to the number 6 carbon atom of the O-3-amino-3-deoxy-α-D-glucopyranosyl ring of the 6'-carbamoyl tobramycin molecule having been derivatized with the $-C(O)NH_2$ group. Thus, the person skilled in the art would understand that, as used in the specification, "6'-O-carbamoyl tobramycin" refers to the compound named as 6"-O-carbamoyl tobramycin in the tobramycin prior art, such as Koch et al., *The Journal of Antibiotics*, 1973, vol. 26, pp. 745-751 (in particular, see the structure of Nebramycin factor 5' in page 749 and the last sentence in page 751) cited in the Information Disclosure Statement filed on March 20, 2003. In order to more expressly disclose the meaning of "6'-O-carbamoyl tobramycin" page 4 of the specification is amended by inserting --The term "6'-O-carbamoyl tobramycin" used herein means the compound referred to as 6"-O-carbamoyl tobramycin in the prior art--. Applicants submit that the insertion does not create any new matter because the information inserted would have been apparent to one skilled in the art based on the specification as filed.

Applicants respectfully traverse the indefiniteness rejection of claim 19 because the Office Action was incorrect in alleging that the only mineral salt recited in the Markush group is zinc phosphate. According to page 5, line 7, of the specification, "zinc phosphate" should have been "zinc, phosphate". The typographical error of "zinc phosphate" is corrected with the amendment to claim 19 above. The term "mineral salt" is defined in page 4, lines 7-9, of the

specification with salts of zinc and salts of phosphate given as examples.

Applicants respectfully traverse the indefiniteness rejection of claim 23 based on the Office Action's allegation that "wherein the inorganic phosphate is fed during fermentation" lacks antecedent basis because the Office Action interprets claim 20 as pertaining to pH adjustment of the glucose solution prior the glucose solution being added to the fermentation medium. Applicants contend that claim 20 should be interpreted to mean that a glucose solution having a pH of between about 4.0 to about 5.0 is fed in step b) to regulate the constant level of the assimilable carbon source in the fermentation broth. According to claims 21 and 22, the pH of the glucose solution fed in step b) is adjusted using an inorganic phosphate so the pH-adjusted glucose solution contains the inorganic phosphate. Thus, the recitation "wherein the inorganic phosphate is fed during the fermentation" in claim 23 has antecedent basis because, as the pH-adjusted glucose solution is fed during the fermentation in step b) in claim 23, the inorganic phosphate is also fed during the fermentation.

Claim Rejections -- 35 U.S.C. 112, First Paragraph

Applicants respectfully traverse the rejection that claims 24 and 25 were not enabled because the specification does not disclose the information concerning the deposits of the *Streptomyces tenebrarius* strain NCAIM B(P) 000169 and the *Streptomyces tenebrarius* strain NCAIM B(P) 000204. To advance prosecution, applicants have amended page 6 of the specification by providing the name and address of NCAIM, an International Depositary Authority, and the date when the deposits of the two *Streptomyces tenebrarius* strains having

accession numbers NCAIM B(P) 000169 and NCAIM B(P) 000204 were made under the Budapest Treaty for patent purposes. Applicants state that all restrictions, if any, on the availability to the public of the deposited materials will be irrevocably removed upon the granting of a patent. Withdrawal of the non-enablement rejections of claims 24 and 25 is requested.

Claim Rejections -- 35 U.S.C. 102(b)

Applicants respectfully traverse the anticipatory rejections of claims 1-6, 9-11, 18, 19, 26 and 27 over Dinkov (Bulgarian Patent Publication No. BG 50996).

The processes of claims 1-6, 9-11, 18, 19, 26 and 27 prepare 6'-O-carbamoyl tobramycin comprising, among other steps, regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth.

Dinkov discloses a process for preparing tobramycin by cultivating a strain of *Streptomyces tenebrarius*, ATTC 17920. In the process of Dinkov, a limiting substrate composition containing glucose, carbamide, calcium pantothenate, sodium glutamate and KCl is added **batch-wise** in an amount of **15 to 35%** by volume of the culture liquid to maintain the concentrations of glucose in the range of 0.5% to 1.5% and ammonia nitrogen in the range of 0.010% to 0.020% (see the second full paragraph of page 5 and the paragraph bridging pages 5 and 6, of USPTO's English translation of BG 50996; emphasis added).

The **batch-wise** feeding performed in the process of Dinkov differs from the processes of claims 1-6, 9-11, 18, 19, 26 and 27 at least in failing to regulate constant levels of the assimilable

carbon source and assimilable nitrogen source in the fermentation broth. The process of Dinkov results in significant up-and-down swing of the concentrations of the assimilable carbon source and assimilable nitrogen source in the fermentation broth. Page 5 of the Office Action alleges that this assertion of the applicants is a bald assertion. Applicants respectfully disagree. The calculations described below will show that applicants have had a technical reason to support the statement that the process of Dinkov results in significant up-and-down swing of the concentrations of the assimilable carbon source and assimilable nitrogen source in the culture liquid.

To illustrate this point, applicants have performed the calculations below using glucose as an example of one of the ingredients in the limiting substrate composition used by Dinkov. Dinkov discloses that the size of each batch of the limiting substrate composition added in the batch-wise feeding is **15 to 35%** of the culture liquid. The limiting substrate composition of Dinkov contains glucose at a concentration ranging from **4.0% to 7.5%** (page 5, the 7th line from the bottom, English translation of BG 50996). In order to calculate the lower limit of a jump in the glucose concentration of the culture liquid of Dinkov resulting from the addition of a batch of the limiting substrate composition of Dinkov, the calculations here assume that each batch added by Dinkov is of the minimal batch size of 15% containing the minimal glucose concentration of 4.0%. Since the fermentation process of Dinkov is aimed at achieving a target glucose concentration of 0.5% to 1.5% in the culture liquid (page 6, line 2, of the English translation of BG 50996), it is reasonable to assume that Dinkov adds a batch of the limiting substrate composition whenever the glucose concentration of the culture liquid has dropped down, due to

metabolic glucose consumption by the microbe, to no lower than 0.5%, and more likely whenever the glucose concentration of the culture liquid has dropped down to higher than 0.5% in order to compensate for potential time lag in the addition of the batch of the limiting substrate composition. In the calculations here, applicants assume that Dinkov adds a batch of the limiting substrate composition to the culture liquid when the glucose concentration of the culture liquid has dropped down to 0.6%. For each ml of culture liquid originally present in the fermentation vessel used by Dinkov, at a batch size of 15% by volume, 0.15 ml of the limiting substrate composition is added (because 15% of 1 ml is 0.15 ml) leading to a final volume of 1.15 ml of the resulting culture liquid. The 0.15 ml batch of the limiting substrate composition added would contain 6 mg of glucose (because 0.15 ml x 4% = 0.15 ml x 4 g/100 ml = 6 mg). The 6 mg of glucose added would increase the glucose concentration in the resulting culture liquid by 5.2 mg/ml or 0.52% (because 6 mg/1.15 ml = 5.2 mg/ml). Thus, the addition of the smallest batch of the limiting substrate composition allowed in the process of Dinkov would lead to a sudden increase in the glucose concentration in the culture liquid by 0.52%, which almost instantaneously doubles the glucose concentration in the culture liquid to reach 1.12%. After the batch of the limiting substrate composition is added, the glucose concentration in the culture liquid would decrease with time due to glucose consumption by the microbe until the glucose concentration in the culture liquid drops to 0.6%. Then the batch-wise feeding is repeated with the addition of a second batch of the limiting substrate composition causing the glucose concentration of the culture liquid to almost double instantaneously (jumping by 0.52% to reach 1.12%). The up-and-down swing of the glucose concentration in the culture liquid continues until

the fermentation is stopped and the tobramycin is harvested in the process of Dinkov. Thus, even assuming the smallest batch size of the limiting substrate composition containing the lowest level of glucose permitted by Dinkov, the batch-wise feeding process of Dinkov causes significant up-and-down swing of the glucose concentration in the culture liquid. The batch-wise feeding process of Dinkov does not regulate constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth as required by step b) of claim 1. Applicants maintain that Dinkov fails to anticipate claims 1-6, 9-11, 18, 19, 26 and 27.

An additional reason why Dinkov fails to anticipate claims 5, 6, 9 and 10 is that Dinkov maintains the glucose concentration in the culture liquid to be 0.5% to 1.5% and Dinkov also adds sodium glutamate in the limiting substrate composition. The level of the assimilable carbon source in the culture liquid maintained by Dinkov is much higher than the constant level of about 0.01 to about 0.4% recited in claim 5, about 0.001 to about 0.05% recited in claim 6, about 0.005 to about 0.1% recited in claim 9 and about 0.001 to about 0.1% recited in claim 10.

An additional reason why Dinkov fails to anticipate claim 14 is that Dinkov maintains the ammonia nitrogen concentration in the culture liquid to fall within the range of 0.010% to 0.020%. In contrast, claim 14 recites a constant level of ammonia nitrogen of about 0.03 to about 0.2%.

Another reason why Dinkov fails to anticipate claims 18 and 19 is that Dinkov does not continuously feed a mineral salt into the culture liquid.

Claim Rejections - 35 U.S.C. § 103(a)

Applicants respectfully traverse the obviousness rejections of claims 1-27 over Dinkov taken with Ott et al. (GB 2,114,978) or Tomita et al. (US 4,032,404).

Applicants disagree with the Office Action's allegation that Dinkov teaches a fermentation process for producing 6'-O-carbamoyl tobramycin by regulating constant levels of the assimilable carbon source and assimilable nitrogen source (see page 4, third full paragraph of the Office Action). As explained above, in the process of Dinkov, the concentration of the assimilable carbon source in the culture liquid moves up and down by at least 0.52% through the cycle of batch-wise feeding, instead of being regulated at constant levels as recited in claim 1. Dinkov differs from claims 1-27 at least in not teaching a fermentation process for producing 6'-O-carbamoyl tobramycin by regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the broth.

Ott et al.discloses a batch-mode fermentation process for producing 6'-O-carbamoyl tobramycin by incubating a nutritive medium containing a 6'-O-carbamoyl tobramycin producing strain MNG204 of *Streptomyces tenebrarius*, and organic carbon and nitrogen sources in a submerged, aerated culture in a shaker until a substantial amount of 6'-O-carbamoyl tobramycin is accumulated (page 2, lines 27-38; page 3, lines 4, 5 and 14; page 4, line 15). Ott et al. does not teach or suggest regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation liquid. Thus, Ott et al does not cure the deficiency of Dinkov concerning claims 1-27. Claims 1-27 would not have been obvious over Dinkov taken with Ott et al.

Tomita et al.discloses a fermentation process for producing 6'-O-carbamoyl tobramycin

by culturing a strain of 6'-O-carbamoyl tobramycin producing *Streptoalloteichus hindustanus* in an aqueous nutrient medium containing assimilable sources of carbon and nitrogen (column 10, line 64 to column 11, line 5 and column 11, lines 32-37). Tomita et al. differ from claims 1-27 at least in not teaching or suggesting regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth. Tomita et al fails to cure the deficiency of Dinkov regarding claims 1-27. Claims 1-27 would not have been obvious over Dinkov taken with Tomita et al.

An additional reason why Dinkov taken with Ott et al. or Tomita et al. fail to render obvious claims 5, 6, 9 and 10 is that Ott et al. or Tomita et al. does not teach or suggesting a way to remedy the deficiency of Dinkov by regulating constant level of the assimilable carbon source in the culture liquid as recited in claims 5, 6, 9 and 10.

An additional reason why Dinkov taken with Ott et al. or Tomita et al. fail to render obvious claim 14 is that Ott et al. or Tomita et al. does not teach or suggest regulating constant level of the assimilable nitrogen source in the fermentation broth to about 0.03 to about 0.2% recited in claim 14. Ott et al. used a concentration of the assimilable nitrogen source at 0.4 to 0.6%, and is not regulated constant (see page 4). Tomita et al. used a concentration of the assimilable nitrogen source at 0.3%, and is not regulated at a constant level (see column 14, lines 4, 37 and 49).

Another reason why Dinkov taken with Ott et al. or Tomita et al. fail to render obvious claims 16 and 17 is that Ott et al. or Tomita et al. does not teach or suggest a way to cure the deficiency of Dinkov by continuously feeding glucose, sodium glutamate and ammonium sulfate

to regulate constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth.

Another reason why Dinkov taken with Ott et al. or Tomita et al. fail to render obvious claim 17 is that Ott et al. or Tomita et al. does not teach or suggest a way to cure the deficiency of Dinkov by continuously feeding glucose, sodium glutamate and ammonium sulfate independently.

Another reason why Dinkov taken with Ott et al. or Tomita et al. fail to render obvious claims 18 and 19 is that Ott et al. or Tomita et al. does not teach or suggest continuously feeding a mineral salt into the fermentation broth.

Another reason why Dinkov taken with Ott et al. or Tomita et al. fail to render obvious claims 20-23 is that Ott et al. or Tomita et al. does not teach or suggest a way to cure the deficiency of Dinkov by feeding a glucose solution at a pH between about 4.0 to about 5.0.

Further reasons why Dinkov taken with Ott et al. or Tomita et al. fail to render obvious claims 21-23 is that Ott et al. or Tomita et al. does not teach or suggest a way to cure the deficiencies of Dinkov by adjusting the pH of the glucose solution with an inorganic phosphate, such as phosphoric acid, or by adjusting the pH of the glucose solution with a phosphoric acid by feeding the glucose solution containing the phosphoric acid in a quantity of about 0.001 to about 0.002% per day.

Dinkov taken with Ott et al. or Tomita et al. fail to render obvious claims 24 and 25 because Ott et al. or Tomita et al. does not teach or suggest a way to cure the deficiency of Dinkov by using *Streptomyces tenebrarius* strain NCAIM B(P) 000169 or NCAIM B(P) 000204

recited in claims 24 and 25.

Applicants also note that the process of the instant claims can achieve, unexpectedely, much higher yields than fermentation processes that do not regulate constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth (see Examples 4 and 5 in the specification).

Withdrawal of the obviousness rejections is requested.

Conclusion

If the Examiner deems that there are issues that can be resolved by a telephone interview, the Examiner is urged to telephone the undersigned.

In the event that this paper is deemed not timely, applicants petition for an appropriate extension of time. The petition fee and any other fees that may be required in relation to this paper can be charged to Deposit Account No. 11-0600, referencing the Attorney Docket No. 02664/47002.

Respectfully Submitted,

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King L. Wong

King L. Wong
Reg. No. 37,500

KENYON & KENYON LLP
1500 K Street, N.W., #700
Washington, DC 20005
(202) 220-4220